

UTILITY PATENT APPLICATION
UNDER 37 CFR 1.53(b)

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Washington D.C. 20231

Case Docket No. 114232.104

Sir:

Transmitted herewith for filing is the patent application of:

INVENTOR: Leland SHAPIRO

FOR: METHODS AND COMPOSITIONS USEFUL IN INHIBITING APOPTOSIS

Enclosed are:

- 32 pages of specification, claims, abstract
- Declaration & Power of Attorney
- Priority Claimed to US Provisional Application No. 60/123,167 filed March 5, 1999
- Certified copy of _____
- 2 sheets of formal drawing
- An assignment of the invention to The Trustees of University Technology Corporation and the assignment recordation fee
- Return Receipt Postcard
- Information Disclosure Statement, Form PTO-1449
- Copies of IDS Citations
- Verified Statement Claiming Small Entity Status

The filing fee has been calculated as shown below:

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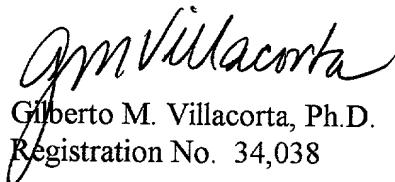
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Respectfully submitted,

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March 3, 2000
#142455

Docket No.: 114232.104

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :
Leland SHAPIRO :
Serial No. :
Filed: :
For: **METHODS AND COMPOSITIONS USEFUL IN INHIBITING APOPTOSIS**
:

**TRANSMITTAL OF VERIFIED STATEMENT
CLAIMING SMALL ENTITY STATUS**

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Transmitted herewith for filing in the above-referenced application is the following:

VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS-

SMALL BUSINESS CONCERN

Respectfully submitted,

Pepper Hamilton LLP

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Date: March 3, 2000
DC #142460 v1 (31X8011 WPD)

Applicant or Patentee: Leland Shapiro

Attorney's Docket No.: 114232.104

Serial or Patent No.: _____

Filed or Issued: _____

For: METHODS AND COMPOSITIONS USEFUL IN INHIBITING APOPTOSIS

**VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(f) and 1.27(c)) - SMALL BUSINESS CONCERN**

I hereby declare that I am

the owner of the small business concern identified below:
 an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF ORGANIZATION: University Technology Corporation

ADDRESS OF ORGANIZATION: 3101 Iris Avenue, Suite 250, Boulder, CO 80301

I hereby declare that the above identified small business concern qualified as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, oral third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled METHODS AND COMPOSITIONS USEFUL IN INHIBITING APOPTOSIS by inventor(s) Leland Shapiro described in

[X] the specification filed herewith.
 [] application Serial No. _____, filed _____.
 [] patent no. , issued .

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e). *NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME _____

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INDIVIDUAL

SMALL BUSINESS CONCERN

NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

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TITLE IN ORGANIZATION: _____

ADDRESS OF PERSON SIGNING: _____

SIGNATURE: Leland Shapiro

DATE: 27/29/2000

METHODS AND COMPOSITIONS USEFUL IN INHIBITING APOPTOSIS

The present application claims the priority of U.S. application serial no.

5 60/123,167, filed March 5, 1999, the entire disclosure of which is incorporated by reference herein.

1. FIELD OF THE INVENTION

The present invention relates to compositions and methods useful in the inhibition 10 of apoptosis. Likewise, the present invention relates to methods of treating diseases associated with excessive or unregulated apoptosis.

2. BACKGROUND OF THE INVENTION

Normal development, growth, and function of multi-cellular organisms require 15 control both of processes that produce cells and of those that destroy cells. Mitosis, or cell proliferation, is highly regulated except in specific states termed cell proliferative diseases. There also exist processes for destruction of cells. Cells in multi-cellular organisms die by two distinct mechanisms. One method, termed necrotic cell death, is characterized by cytoplasmic swelling, rupturing of cellular membranes, inflammation 20 and disintegration of subcellular and nuclear components. The other method, apoptosis, by contrast, is characterized by more organized changes in morphology and molecular structure. Apoptotic cells often condense and shrink, in part, by cytoplasmic membrane blebbing, a process of shedding small packets of membrane-bound cytoplasm. The chromosomes of such cells condense around the nuclear periphery. Generally, in 25 apoptotic cells the chromosomes are degraded by specific nucleases that cleave DNA to produce regular-sized fragments. Importantly, there is a requirement for new mRNA and protein expression during the early stages of some forms of apoptosis, indicating that it is an active process. Macrophages envelop and phagocytose apoptotic cells, thereby digesting and recycling the cellular components.

30 Changes in cell morphology during apoptosis are profound. Detection of the many morphological changes associated with apoptosis is detected using light

microscopy or electron microscopy. In particular, electron microscopy is useful for evaluating cells with a high nucleus to cytoplasm ratio and light microscopy is useful for immuno-and histochemistry. The changes characteristic of apoptosis include decreased volume, compaction of cytoplasmic organelles, and increased cell density. In addition, 5 microvilli disappear, blebs of cytoplasm form at the cell surface, and the blebs dissociate from the cell to form apoptotic bodies. Other techniques are useful in the analysis of apoptosis including confocal, laser, and scanning microscopy, fluorescent DNA dye binding, and molecular techniques. The molecular techniques permit detection of apoptosis in formalin-fixed and embedded tissue, including terminal deoxynucleotidyl 10 transferase (TdT)-mediated dUTP-biotin nick end labeling (TUNEL) and *in situ*, end labeling (ISEL).

Protease Involvement

The progression of apoptosis requires the coordinated action of specific proteases. The proteases can be inhibited by inhibitors including N-tosyl-L- 15 phenylalanylchloromethyl ketone (TPCK) and N-tosyl-L-lysylchloromethyl ketone (TLCK). Furthermore, at least 10 cysteine proteases related to interleukin-1- β converting enzyme have been identified as components of apoptotic signaling pathways. The interleukin-1- β converting enzyme-like proteases are referred to as caspases and are identified and have been isolated by molecular cloning.

20 In addition, there are other proteases involved in apoptosis including the granzymes and cathepsin. Granzyme B is a serine esterase that can activate several members of the caspase family. Granzyme B may be a mediator of cytotoxic T lymphocyte induced apoptosis. Granzyme B is known to cleave and initiate caspase 3, a likely component of its mode of action. Granzyme B may also initiate nuclear events 25 associated with cytotoxic T lymphocyte-induced apoptosis, consistent with observations that it is passively transported into the nucleus and bind to nuclear proteins. One action of Granzyme B may be in the regulation of conversion of proCPP32 to CPP32. CPP32 is itself a protease thought to cleave poly(ADP-ribose) polymerase (PARP) and may also activate prolamain protease resulting in activation of lamin protease. Cleavage of lamins 30 and inactivation of the DNA repair enzyme PARP promote the development of apoptotic changes in the cell nucleus.

Serine Proteases

In contrast to cysteine proteases, the role of serine proteases in apoptosis is controversial. For a general discussion, see Kaufmann, S. *Cancer Res* 1993, 53, 3976. For example, it is known that the serine protease inhibitor TLCK inhibits apoptosis-
5 associated proteolysis. However, TLCK is known to inhibit cysteine proteases in addition to serine proteases, and has recently been shown to inhibit a member of the interleukin-1 β converting enzyme family. Thus, the effect of TLCK on apoptosis is likely not mediated by an effect as a serine protease inhibitor, given the more established role of cysteine proteases in apoptosis.

10 *Cellular Protease Targets*

Multiple polypeptide species must be modified to produce the wide range of morphological manifestations that characterize apoptosis. For example, the lamins are nuclear intermediate filament proteins that form a fibrous layer between the inner nuclear membrane and the chromatin. The resulting lamina is thought to play a role in maintaining nuclear shape and in mediating chromatin-nuclear membrane interactions.
15 Thus, the apoptosis-associated changes in nuclear shape might require lamin reorganization. Another polypeptide that is cleaved during apoptosis is poly (ADP-ribose) polymerase (PARP). PARP is an abundant nuclear enzyme that catalyzes the conversion of the dinucleotide NAD $^+$ to nicotinamide and protein-linked chains of ADP-ribose. Yet, the detailed role of PARP in the process of apoptosis is unclear. Studies
20 have suggested that inhibitors of PARP delay apoptosis and yet other studies have suggested that inhibition of PARP increases the fragmentation of DNA during apoptosis. It is clear, however, that PARP is proteolytically degraded late in apoptosis.

Another proteolytic enzyme target during apoptosis is the U1 ribonuclear protein (U1-70k), a molecule required for splicing of precursor mRNA that is itself cleaved to an inactive 40 kDa fragment during apoptosis. The cleavage of this polypeptide would result in cessation of RNA processing.

Other substrates for protease activity during apoptosis include fodrin, the PITSLRE β 1 protein kinase, the adenomatous polyposis coli (APC) protein, the
30 retinoblastoma gene product, terminin, and nuclear matrix proteins. Cleavage of fodrin, an abundant membrane associated cytoskeletal protein, has been detected during

apoptosis in a variety of cell lines. PITSLRE β 1 protein kinase, a member of the P34^{cdc2} gene family has been shown to induce mitotic delay in CHO cells. Members of this family appear to be cleaved during apoptosis. For example, recent studies indicate that PITSLRE β 1 kinase is proteolytically cleaved during FAS- or steroid- induced apoptosis
5 in T-cells. Another major group of protease targets is the caspases, themselves proteases, or precursor forms of caspases. Yet another group of proteins which may well be downstream effectors of caspase-mediated apoptosis, include the protein kinases PKC δ , PKC θ , MEKK1, the sterol regulatory element binding proteins 1 and 2, and the DNA fragmentation factor (DFF).

10 *Diseases associated with Apoptosis*

Increased levels or apparent induction of apoptosis is associated with a number of diseases including cancer, autoimmune diseases including rheumatoid arthritis, neurodegenerative diseases, myocardial infarction, stroke, sepsis, ischemia-reperfusion injury, toxin induced liver injury, and AIDS (see Kidd, V.J., *Annu Rev Physiol*, **1998**, *60*, 15 533; List, P.J.M., et al., *Arterioscler Thromb Vasc Biol* **1999**, *19*, 14; Jabs, T., *Biochem Pharmacol* **1999** *57*, 231; Deigner, H.P., et al. *Curr Med Chem* **1999**, *6*, 399). The apoptosis appears to be mediated by oxygen free radicals [O \cdot] which have been implicated in various disorders including atherosclerosis, diabetes, sepsis, Alzheimer's disease, arthritis, muscular dystrophy, cancer, Downs syndrome, multiple sclerosis, HIV infection and other inflammatory diseases (Morel, J. B. and Dangle, J.L., *Cell Death Differ* **1997**, *4*, 671; Beal, M. F., *Curr Opin Neurobiol* **1996**, *6*, 661).

3. SUMMARY OF THE INVENTION

The present invention is directed to a method of treating an animal or a patient suffering from a disease characterized by excessive apoptosis. The method of the invention comprises administering a therapeutically effective amount of at least one serine protease inhibitor and subsequently monitoring a decrease in apoptosis.

In a preferred embodiment, the animal is a human. In another preferred embodiment, the agent is α_1 -antitrypsin (ATT) or an α_1 -antitrypsin-like agent. In addition, peptides of interest are homologous and analogous peptides. All homologues are natural peptides which have sequence homology, analogs will be peptidyl derivatives,

e.g., aldehyde or ketone derivatives of such peptides. Furthermore, agents with α_1 -antitrypsin-like activity are also envisioned. In this regard, peptide derivatives of α_1 -antitrypsin, compounds like oxydiazole, thiadiazole, CE-2072, UT-77, and triazole peptoids are preferred. The α_1 -antitrypsin-like agent includes, but is not limited to, small 5 organic molecules including naturally occurring, synthetic, and biosynthetic molecules, small inorganic molecules including naturally-occurring and synthetic molecules, natural products including those produced by plants and fungi, peptides, variants of α_1 -antitrypsin, chemically modified peptides, and proteins. It is a further embodiment of this invention that an individual with risk for a pathological disease or condition that is 10 precipitated at least in part by excessive apoptosis, can be treated to prevent the onset of acute disease with a prophylactic treatment of an agent exhibiting α_1 -antitrypsin or α_1 -antitrypsin-like activity.

A further embodiment of the invention envisions a method for inhibiting apoptosis in an in vitro mammalian cell culture, an ex vivo mammalian tissue culture, or 15 a mammalian organ, comprising providing to a cell culture, tissue culture, or organ, an amount of a serine protease inhibitor sufficient to inhibit apoptosis in the cell culture, tissue culture, or organ. In the aforementioned embodiment, a measured amount of apoptosis is indicative of expression or activity of apoptosis.

A still further embodiment of the invention directed to a method of inhibiting 20 apoptosis comprises allowing a serine protease inhibitor to bind to a protease and measuring the decrease in apoptosis. Another embodiment of the invention is directed to a method of inhibiting apoptosis comprising allowing a serine protease inhibitor to bind to a cell surface receptor and measuring the decrease in apoptosis.

A yet still further embodiment of the invention is directed to use of oxidation- 25 resistant and free-radical resistant inhibitors of serine proteases. In this regard, the oxidation-sensitive Met³⁵⁸ in α_1 -antitrypsin can, by genetic engineering, be replaced by Val³⁵⁸- α_1 -antitrypsin, which results in a molecule termed Val³⁵⁸- α_1 -antitrypsin. Val³⁵⁸- α_1 -antitrypsin is a more potent inhibitor of neutrophil elastase than is Met³⁵⁸- α_1 -antitrypsin possibly because of the stability of Val³⁵⁸- α_1 -antitrypsin to the neutrophil oxidative burst. 30 The Met at position 358 is replaced with any hydrophobic or neutral oxidation-resistant

amino acid residue, including: alanine, asparagine, α -amino butyric acid, anthranilic acid, β -cyanoalanine, β -(3,4-dihydroxyphenyl) alanine, 3,5-diiodotyrosine, glutamine, glycine, homoserine, 3-hydroxyanthranilic acid, 5-hydroxy-indole-3-acetic acid, 3-hydroxykynurenine, hydroxyproline, 5-hydroxy-tryptophan, indoleacetic acid, 3-iodotyrosine, isoleucine, allo-isoleucine, leucine, leucylglycine, norleucine, norvaline, phenylalanine, proline, prolylglycine, serine, threonine, allo-threonine, throxine, 3,5,3'-tri-iodo-thyronine, tryptophan, and tyrosine. The amino acid substitutions are effected by genetic engineering, chemical modification, or a combination thereof.

10 4. BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 illustrates the effect of α_1 -antitrypsin on apoptosis in primary rat brain cerebral granule cells.

15 FIG. 2 illustrates the effect of α_1 -antitrypsin and the peptoid CE-2072 on apoptosis in RCG Neuron (rat cerebral granule) cells, also termed RCGC.

20 5. DETAILED DESCRIPTION OF THE INVENTION

5.1 STANDARD METHODS

In accordance with the present invention there can be employed conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of the art. Such techniques are explained fully in the literature. See, e.g., Sambrook, Fritsch & Maniatis, *Molecular Cloning: A Laboratory Manual, Second Edition 1989*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; *Animal Cell Culture*, R. I. Freshney, ed., 1986).

25 5.2 SERINE PROTEASE INHIBITORS

The current invention teaches methodologies and agents for treating animals and patients that suffer from a disease involving excessive apoptosis. The methods involve administration of therapeutically effective amounts of at least one serine protease inhibitor and testing for changes in apoptosis by any of several means known in the art. The serine proteases that are inhibited by the agent of the invention include trypsin, elastase, cathepsin G, tryptase TL-2, Factor Xa and proteinase-3. The methods further involve inhibition of oxygen free radicals and inhibition of oxygen free radical formation

by serine protease inhibitors. The method further includes a pharmaceutically acceptable carrier, any of which are known in the art. Serine protease inhibitors include α_1 -antitrypsin, or α_1 -antitrypsin-like agents. In the latter group are included the oxydiazole, thiazole, triazole peptoids, or some combination of these agents. The serine 5 protease inhibitor is optionally derivatized chemically by esterification, acetylation or amidation.

There are numerous diseases that are characterized by excessive apoptosis. Among these diseases are cancer, autoimmune diseases, neurodegenerative diseases, myocardial infarction, stroke, ischemia-reperfusion injury, toxin-induced liver injury, 10 sepsis and AIDS.

A preferred embodiment of the invention is directed toward the treatment of myocardial infarction. Another preferred embodiment of the invention is directed toward treatment of stroke, also known as brain ischemia or cerebrovascular accident. The therapeutically effective amounts of the serine protease inhibitors are sufficient to bring 15 the concentration of the added agent in the biological fluid of the individual to between about 10 pM and 2 mM. For α_1 -antitrypsin the effective concentrations correspond to between about 5 nanograms per milliliter to about 10 milligrams per milliliter of the biological fluid of the individual. The biological fluid of the individual is calculated from the total body weight of the individual or, in diseases that are localized to specific body 20 compartments, from the volume of the compartment. Biological fluid can include, but is not limited to, blood, plasma, serum, lymph, tears, saliva, cerebrospinal fluid, or combinations thereof.

In a preferred embodiment of the invention, the therapeutically effective amount is sufficient to bring the concentration in the biological fluid to between 0.5 μ M and 200 μ M, preferably between 5 μ M and 200 μ M, most preferably about 100 μ M. The agent is advantageously administered according to the weight of the subject. Administration of 25 the therapeutically effective amount of serine protease inhibitor can be in a bolus, for example, of about 0.001 to 7 g of α_1 -antitrypsin-like agent or about 1 to 70 g of α_1 -antitrypsin, per kg of body weight of the subject. Preferred amounts are about 0.01 g/kg 30 body weight of oxydiazole, thiazole, or triazole peptoids, and about 1 g/kg body weight of natural or variant α_1 -antitrypsin.

The administration of the agent in the invention can be performed parenterally, orally, vaginally, nasally, buccally, intravenously, intramuscularly, subcutaneously, rectally, intrathecally, epidurally, transdermally, intracerebroventricularly, or combinations thereof.

5 In another embodiment of the invention, the agent is administered continuously or intermittently by osmotic pump or by implanted osmotic pump, including those of the Alza Corporation. It is a further embodiment of the invention that the therapeutically effective amount of the serine protease inhibitor is administered between about once daily to about once hourly. In a more preferred embodiment of the invention, the serine
10 protease inhibitor is administered twice per day. It is a further embodiment of the invention that the monitoring of changes in apoptosis be performed on tissue obtained from an animal or patient. Any of several methods for monitoring apoptosis, well known in the art, are suitable.

15 A further method of the invention is directed to encouraging the binding of a serine protease inhibitor to a protease and observing a change in apoptosis. In this embodiment, the serine protease inhibitor is α_1 – antitrypsin or α_1 – antitrypsin-like agent. The α_1 – antitrypsin-like agent is also a substituted oxydiazole, substituted thiadiazole, substituted triazole peptoids, or any combination of these agents.

20 Apoptosis is associated with free radical production, including oxygen free radicals. Free radicals are known to inactivate natural α_1 -antitrypsin. Therefore, it is desirable to supplement α_1 -antitrypsin in blood with sufficient α_1 -antitrypsin-like activity which is not inactivated by free radicals. Alternatively, a mutant α_1 -antitrypsin resistant to inactivation by free radicals, or administration of a synthetic molecule that is not inactivated by free radicals, is contemplated. Also, co-administration of a free radical
25 scavenger or inhibitor is contemplated.

30 The present invention is not limited by the mechanism of action of α_1 – antitrypsin inhibitors in decreasing apoptosis. Thus the apoptosis may be mediated by tumor necrosis factor, by anti-Fas or by any other mechanism. In a particular embodiment of the invention apoptosis not mediated by tumor necrosis factor is inhibited by the α_1 – antitrypsin-like agents of the invention. Moreover, the agents of the invention are effective to inhibit apoptosis in a plurality of organs including, but not limited to brain,

heart, spinal cord, peripheral nerves, skin, stomach, liver, pancreas, gut, ovaries, testis, and endocrine glands.

It is to be understood that the present invention is not limited to the examples described herein, and other serine protease inhibitors known in the art are used within the 5 limitations of the invention. For example, one skilled in the art can easily adopt inhibitors as described in WO 98/24806, which discloses substituted oxadiazole, thiadiazole and triazole as serine protease inhibitors. U.S. Pat. No. 5,874,585 discloses substituted heterocyclic compounds useful as inhibitors of serine proteases including: (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4- 10 oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-phenylethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L- prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-methoxybenzyl)-1,2,4- 15 oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trifluoromethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L- prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(methyl)-1,2,4- 20 oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L- Valyl-N-[1-(3-(5-(difluoromethyl)-1,2,4-oxadiazolyl) carbonyl)-2-(S)-Methylpropyl]-L- Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(benzyl)-1,2,4- 25 oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L- Valyl-N-[1-(3-(5-(3-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L- Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(2,6-difluorobenzyl)-1,2,4- 30 oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L- Valyl-N-[1-(3-(5-(trans-styryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L- Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(trans-4-Trifluoro methylstyryl)- 1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L- Valyl-N-[1-(3-(5-(trans-4-Methoxystyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)- 35 Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(3- Thienylmethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(Phenyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; and (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(3- 40 Phenylpropyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide. U.S.

Patent No. 5,216,022 teaches other small molecules useful for the practice of this invention, including: Benzyloxycarbonyl-L-valyl-N-[1-(2-[5-(3-methylbenzyl)-1,3,4-oxadiazolyl] carbonyl)-2-(S)-methylpropyl]-L-prolinamide (also known as CE-2072), Benzyloxycarbonyl-L-valyl-N-[1-(2-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; Benzyloxycarbonyl-L-valyl-N-[1-(2-(5-(methyl)-1,3,4-oxadiazolyl]carbonyl)- 2-(S)-methylpropyl]-L-prolinamide; Benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(3-trifluoromethylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(4-Dimethylamino benzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; Benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(1-naphthyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-[1-(3-(5-(3,4-methylenedioxybenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; Benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethoxybenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-difluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl] carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(biphenylmethine)-1,2,4-oxadiazolyl] carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-phenylbenzyl)-1,2,4-oxadiazolyl] carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenoxybenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(cyclohexylmethylen)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethyldimethylmethylen)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(1-naphthylmethylen)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-pyridylmethyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-

diphenylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-dimethylaminobenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; 2-(5-[(Benzylloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)- (S)-2-methylpropyl]acetamide; 2-(5-Amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(3-(5- (3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 2-(5-[(Benzylloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-(S)-2-methylpropyl]acetamide; 2-(5-Amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5- (3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-methylpropyl]acetamide; (Pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide; (Pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)]-1,2,4-oxadiazolyl)-(S)-methylpropyl]amide; (2S,5S)-5-Amino-1,2,4,5,6,7-hexahydroazepino-[3,2,1]-indole-4-one-carbonyl -N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-(R,S)-2-methylpropyl]amide; BTD-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide; (R,S)-3-Amino-2-oxo-5-phenyl-1,4,-benzodiazepine-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; (Benzylloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide; (Benzylloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide; Acetyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide; 3-(S)-(Benzylloxycarbonyl)amino- ϵ -lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3-(S)-(Amino)- ϵ --lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide trifluoroacetic acid salt; 3-(S)-[(4-morpholino carbonyl-butanoyl)amino]- ϵ --lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(R,S)-methylpropyl]acetamide; 6-[4-Fluorophenyl]- ϵ -lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 2-(2-(R,S)-Phenyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-

methylbenzyl)-1,3,4 -oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 2-(2-(R,S)-phenyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4 -oxadiazolyl]hydroxymethyl)-2-(S)-methylpropyl]acetamide; 2-(2-(R,S)-Benzyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4 -oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-acetamide; 2-(2-(R,S)-Benzyl-4-oxothiazolidin-3-yl oxide]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2- (R,S,)-methylpropyl]acetamide; (1-Benzoyl-3,8-quinazolinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; (1-Benzoyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

10 (1-Phenyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; [(1-Phenyl-3,6-piperazinedione)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4 -oxadiazolyl]carbonyl)]-2-(S)-methylpropyl]acetamide; 3-[(Benzylloxycarbonyl)amino]-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3-

15 [(Benzylloxycarbonyl)amino]-7-piperidinyl-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3-(Carbomethoxy-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3-(Amino-quinolin-2-one)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3-[(4-Morpholino)aceto]amino-

20 quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1, 3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3,4-Dihydro-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-Acetyl-3-(4-fluorobenzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-Acetyl-3-(4-dimethylamino benzylidene)piperazine-2,5-

25 dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-Acetyl-3-(4-carbomethoxy benzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-Acetyl-3-[(4-pyridyl)methylene]piperazine-2,5-dione-N-[1-(2-(5-(3-methyl benzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Benzyl-3-(R)-benzyl-piperazine-2,5,-dione]-N-[1-(2 -[5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Benzyl-3-(S)-benzyl piperazine-2,5,-dione]-N-[1-(2-(5-(3-

methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Benzyl-3(R)-benzylpiperazine-2,5,-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Benzyl-3-(S)-benzylpiperazine-2,5,-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Benzyl-3-(S)-benzylpiperazine-2,5,-dione]-N-[1-(3-(5-(2-dimethylaminoethyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Methyl-3-(R,S)-phenylpiperazine-2,5,-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[-Methyl-3-(R,S)-phenyl piperazine-2,5,-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-(4-Morpholino ethyl)3-(R)-benzyl piperazine-2,5,-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(R,S)-Phenyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(R)-Benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(S)-Benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(S)-Benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1 ,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(R)-Benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1 ,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-Benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1 ,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; and 1-Benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethyl benzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide among others.

25 Yet another embodiment of the invention is directed toward the inhibition of apoptosis resulting from the interaction between a serine protease inhibitor and a cell surface receptor and resulting in a measurable decrease in apoptosis. The serine protease inhibitor of this embodiment is an α_1 – antitrypsin or an α_1 – antitrypsin-like agent. The α_1 – antitrypsin-like agents includes substituted oxydiazoles, substituted thiadiazole, 30 substituted triazole peptoids, or combinations of these agents. The substituted oxydiazole,

thiadiazole, and triazole peptoids are synthesized de novo or derivatized from existing compounds.

5.3. DISEASES ADDRESSED BY THE INVENTION

Specific diseases or disorders for which the therapeutic methods of the invention are beneficial include wasting diseases of various types. The diseases include cancer, neurodegenerative diseases, myocardial infarction, and stroke. The cancers include bladder, breast, kidney, leukemia, lung, myoloma, liposarcoma, lymphoma, tongue, prostate, and uterine cancers. The method of the invention is also applied to Alzheimer's disease, arthritis, muscular dystrophy, Downs Syndrome, sepsis, HIV infection, multiple sclerosis, arteriosclerosis, diabetes, and arthritis. In fact, the invention is applied to any disease associated with elevated levels of apoptosis.

5.4. MODES OF ADMINISTRATION

Modes of administration of the various therapeutic agents used in the invention are exemplified in the examples below. However, the agents are delivered by any of a variety of routes including: by injection (e.g., subcutaneous, intramuscular, intravenous, intra-arterial, and intraperitoneal), by continuous intravenous infusion, transdermally, orally (e.g., tablet, pill, liquid medicine), by implanted osmotic pumps (e.g., ALZA Corp.), by suppository or aerosol spray.

Those skilled in the art of biochemical synthesis will recognize that for commercial scale quantities of peptides, such peptides are preferably prepared using recombinant DNA techniques, synthetic techniques, or chemical derivatization of biologically or chemically synthesized peptides.

The compounds of the present invention are used as therapeutic agents in the treatment of a physiological, or especially, pathological, condition caused in whole or part by uncontrolled serine protease and apoptosis activity. The peptides or peptoids can be administered as free peptides, free peptoids, or pharmaceutically acceptable salts thereof. The terms used herein conform to those in Budavari, S. (Ed.), "The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals," Merck Company, Inc., twelfth edition. The term "pharmaceutically acceptable salt" refers to those acid addition salts or methyl complexes of the peptides which do not significantly or adversely affect the therapeutic properties including efficacy and toxicity, of the peptides and peptoids.

The peptides and peptoids are administered to individuals as a pharmaceutical composition which, in most cases, will comprise the peptide, peptoid, and/or pharmaceutical salts thereof with a pharmaceutically acceptable carrier. The term “pharmaceutically acceptable carrier” refers to those solid and liquid carriers, which do not significantly or adversely affect the therapeutic properties of the peptides.

The pharmaceutical compositions containing peptides and/or peptoids of the present invention are administered to individuals, particularly humans, either intravenously, subcutaneously, intramuscularly, intranasally, orally, topically, transdermally, parenterally, gastrointestinally, transbronchially, and transalveolarly.

10 Topical administration is accomplished by a topically applied cream, gel, rinse, etc. containing therapeutically effective amounts of inhibitors of serine proteases. Transdermal administration is accomplished by administration of a cream, rinse, gel, etc. capable of allowing the inhibitors of serine proteases to penetrate the skin and enter the blood stream. Parenteral routes of administration include, but are not limited to, direct injection such as intravenous, intramuscular, intraperitoneal, or subcutaneous injection.

15 Gastrointestinal routes of administration include, but are not limited to, ingestion and rectal. Transbronchial and transalveolar routes of administration include, but are not limited to, inhalation, either via the mouth or intranasally, and direct injection into an area, such as through a tracheotomy, endotracheal tube, or aspirated through a respiratory mist. In addition, osmotic pumps are used for administration. The necessary dosage will vary with the particular condition being treated, method of administration, and rate of clearance of the molecule from the body.

6. EXAMPLES

25 The following specific examples are provided to better assist the reader in the various aspects of practicing the present invention. As these specific examples are merely illustrative, nothing in the following descriptions should be construed as limiting the invention in any way. Such limitations are, of course, defined solely by the accompanying claims.

30 6.1. EFFECT OF THERAPY WITH α_1 -ANTITRYPSIN FOLLOWING EXPERIMENTAL MYOCARDIAL INFARCTION OR STROKE

Rats (female, 250-300g each) are randomly assigned to one of four groups:

myocardial infarction control, stroke control, myocardial infarction, and stroke. The rats are subjected to a 30 minute ligation of the coronary arterial supply (for the myocardial infarction group) or the left carotid artery (for the stroke group), followed by release of the ligature. Sham operated controls receive the cut-down and manipulation of the artery

5 but without ligation. Immediately preceding the ligation or sham ligation, half of the animals in each group (by random selection) receive α_1 -antitrypsin (sufficient to achieve a 50 μ M concentration of added agent in the blood, or in the alternative, an amount equal to 10 mg/kg body weight) and the other half receive a body-weight equivalent volume of AAT vehicle, intravenously. The AAT vehicle is phosphate-buffered saline, or

10 optionally, any pharmaceutically acceptable carrier. At twenty-four hours after release of the sham or actual ligation the animals are sacrificed and the hearts and brains removed for analysis of the amount of apoptosis. In other experiments the dosage of α_1 -antitrypsin administered is varied between the amounts necessary to produce a concentration of 10 μ M and 250 μ M in the blood. In general, a concentration of 5 mg/ ml of α_1 -antitrypsin is

15 equivalent to about 100 μ M. In yet other experiments the frequency of administration is varied from once per day to four times per day. Likewise, antielastase and antiproteinase are used.

6.2. ANTI-APOPTOSIS THERAPY FOR SEPTIC SHOCK

Protection of mouse L929 cells from apoptotic effects of TNF are evaluated using:

20 the agents α_1 -antitrypsin; (Benzylloxycarbonyl)-L-Valyl-N-[1-2-3(5-(3- methylbenzyl)-1,3,4-oxadiazolyl)carbonyl]-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(2-Phenylethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; and (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(2-Methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide L929. Cells (10^5 cells/well)

25 are treated with 300 ng/ml of human Tumor Necrosis Factor (TNF) with or without the agent (added one hour prior to TNF addition) at 0.02, 0.1, 0.2, 1.0, 2.0 and 10 mg agent/ml. One day later the cells are stained for viability using 2'-[4-hydroxyphenyl]-5-[4-methyl-1-piperazinyl]-2,5'-bi-1H-benzimidazole and fluorescence analyzed for apoptosis using a Leitz fluorescence microscope. The results are evaluated in terms of

30 the dose response to the agent.

6.3. FREE RADICAL SCAVENGERS AS CO-INHIBITORS OF

APOPTOSIS

Agents that reduce free radical levels do not directly prevent the oxidizing effect of free radicals. Therefore, it is advantageous to administer two or three independently acting agents, as opposed to a single agent. Thus, one preferred embodiment of the 5 process is the co-administration of α_1 -antitrypsin and a free radical scavenger, such as glutathione (1 mg/kg body weight).

6.4. FREE RADICAL SCAVENGERS AS CO-INHIBITORS OF APOPTOSIS

In yet another embodiment of the invention, oxidation-resistant α_1 -antitrypsin 10 variants are used to avoid inactivation by excess free radicals. As an example, synthetic α_1 -antitrypsin or recombinant α_1 -antitrypsin produced with alternative and oxidation-resistant amino acid sequences are embodiments of the invention.

6.5. EFFECT OF AAT AND CE-2072 ON APOPTOSIS IN RCG NEURON CELLS

15 RCG neuronal cells are seeded into cell culture dishes in 400 μ l cell culture medium (Eagle's basal medium, BME) containing 10% (v/v) FBS. At day two the now conditioned medium is removed and the cells are treated for 10 hours as follows:

<u>Group</u>	<u>Condition</u>	<u>Treatment</u>
1.	negative control	conditioned medium with serum
2.	positive control	BME without serum
3.	experimental	BME without serum, with IGF-I (50 ng/ml)
4.	experimental	BME without serum, with lyophilized AAT (50 μ M)
5.	experimental	BME without serum, with soluble AAT (50 μ M)
20	6.	BME without serum, with CE-2072 (60 μ M) in DMSO
7.	diluent control	BME without serum, with vehicle
25	8.	BME without serum, with DMSO

Then the medium is replaced with 4% (w/v) paraformaldehyde, incubated for 15 30 minutes at room temperature, and the cells stained with Hoechst dye 33258 (8 μ g/ml) for 15 minutes at room temperature. The apoptosis in the cells is evaluated using a

fluorescence microscope by an evaluator blinded to the method of treatment. The results are shown in Figure 2.

The apoptosis induced by depletion of serum is blocked by lyophilized α_1 -antitrypsin and by agent CE-2072 (a synthetic inhibitor of serine protease). The latter 5 is formally known as benzyloxcarbonyl-L-valyl-N-[1-(2-[5-(3-methylbenzyl)-1,3,4-oxadiazolyl] carbonyl)-2-(S)-Methylpropyl]-L-prolinamide.

6.6. AMELIORATION OF ISCHEMIA IN DONOR ORGANS DURING TRANSPORT AND TRANSPLANT

Human donor organs, including kidneys, are subject to ischemia during transport, 10 which can last up to several hours. Biopsies (3mm) are removed from the top medial surface of donor kidneys undergoing transport prior to implantation, and grouped by time after removal from the donor: 1-2 hours, 2-4 hours, and greater than 4 hours. Donor kidneys transplanted within one hour serve as the first control and the contralateral kidney serves as the second control. Half of the donor kidneys are treated with α_1 -antitrypsin (10 mg/ml fluid) upon removal from the donor to inhibit apoptosis.

6.7. THERAPY WITH OXIDATION-RESISTANT RECOMBINANT α_1 -ANTITRYPSIN VARIANTS

Val³⁵⁸-antitrypsin and Ile³⁵⁸-antitrypsin are produced from the appropriate nucleotide sequences by methods well known in the art, including construction of a plasmid, 20 transfection of the host *E. coli*, selection of transfected colonies, expansion of the culture, and isolation and purification of the mutant gene product. Amounts of the recombinant agents effective in inhibiting apoptosis, excessive clotting, neutrophil extravasation, ischemia-reperfusion injury, or myocardial damage are applied in an experimental model of myocardial infarction (see Example 6.1, *supra*). Effective amounts are between 0.03 25 and 7 g/kg body weight, for example, about 0.5 g/kg. In some experiments the amount of variant antitrypsin is measured in the blood or other biological fluid. In those tests sufficient variant antitrypsin is administered to provide a concentration of about 1 μ M to about 100 μ M in the blood or biological fluid.

6.8. EFFECT OF α_1 -ANTITRYPSIN ON APOPTOSIS

30 Primary rat brain granule cells are pretreated for one hour in the absence or presence of α_1 -antitrypsin (3.0 mg/ml), followed by replacement of the cell culture medium with

either control medium containing 10% (vol/vol) fetal bovine serum, medium devoid of fetal bovine serum, or medium devoid of fetal bovine serum but containing α_1 -antitrypsin. After 24 hours of culture the level of apoptosis is measured. α_1 -Antitrypsin completely reverses the apoptosis associated with serum depletion, which results in cell
5 death.

Throughout this application various publications and patents are referenced. The disclosures of these publications and patents in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. While the invention has been described in connection with
10 specific embodiments thereof, it will be understood that it is capable of further modifications, and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or
15 customary practice within the art to which the invention pertains and as can be applied to the essential features here before set forth and as follows in the scope of the appended claims.

IT IS CLAIMED:

1. A method of treating a subject suffering a disease characterized by excessive apoptosis comprising:
 - 5 administering a therapeutically effective amount of at least one serine protease inhibitor in which the effective amount inhibits excessive apoptosis.
 2. The method of claim 1 further comprising monitoring a decrease in apoptosis.
 3. The method of claim 1, in which the serine protease inhibitor is α_1 -antitrypsin, an α_1 -antitrypsin-like agent, a variant of α_1 -antitrypsin, an anticithepsin G agent, an antitryptase TL-2 agent, an antifactor Xa agent, an antielastase agent, an antiproteinase-3 agent, or combinations thereof.
 4. The method of claim 3 in which the effective amount is between about 0.3 and about 7.0 g/kg body weight.
 - 15 5. The method of claim 1, in which the serine protease inhibitor is a substituted oxydiazole, thiadiazole, triazole peptoids, or combinations thereof.
 6. The method of claim 5, in which the serine protease inhibitor is derivatized by esterification, acetylation, or amidation.
 7. The method of claim 1, further comprising administering at least one free radical scavenger or inhibitor.
 - 20 8. The method of claim 1, in which the serine protease inhibitor is selected from the group consisting of (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-phenylethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trifluoromethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(methyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(difluoromethyl)-1,2,4-oxadiazolyl) carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(benzyl)-1,2,4-
 - 25 30

oxadiazolyl)carbonyl]-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-
Valyl-N-[1-(3-(5-(3-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-
L-Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(2,6-difluorobenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-
5 Valyl-N-[1-(3-(5-(trans-styryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-
Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(trans-4-Trifluoro methylstyryl)-
1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-
L-Valyl-N-[1-(3-(5-(trans-4-Methoxystyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-
Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(3-
10 Thienylmethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide;
(Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(Phenyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-
methylpropyl]-L-prolinamide; and (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(3-
Phenylpropyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide,
Benzylloxycarbonyl-L-valyl-N-[1-(2-[5-(3-methylbenzyl)-1,3,4-oxadiazolyl] carbonyl)-2-
15 (S)-methylpropyl]-L-prolinamide, Benzylloxycarbonyl-L-valyl-N-[1-(2-(3-methylbenzyl)-
1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; Benzylloxycarbonyl-L-
valyl-N-[1-(2-(5-(methyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-
prolinamide; Benzylloxycarbonyl)-L-valyl-N-[1-(2-(5-(3-trifluoromethylbenzyl)-1,3,4-
oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-
20 valyl-N-[1-(2-(5-(4-Dimethylamino benzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-
methylpropyl]-L-prolinamide; Benzylloxycarbonyl)-L-valyl-N-[1-(2-(5-(1-naphthyl)-
1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-
L-valyl-[1-(3-(5-(3,4-methylenedioxybenzyl)-1,2,4 -oxadiazolyl]carbonyl)-2-(S)-
methylpropyl]-L-prolinamide; Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-
25 dimethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
(Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethoxybenzyl)-1,2,4-
oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-
valyl-N-[1-(3-(5-(3,5-difluoromethylbenzyl)-1,2,4 -oxadiazolyl]carbonyl)-2-(S)-
methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-
30 methylbenzyl)-1,2,4-oxadiazolyl] carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
(Benzylloxycarbonyl)-L-valyl-N-[1-(3-(biphenylmethine)-1,2,4-oxadiazolyl

]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-phenylbenzyl)-1,2,4-oxadiazolyl] carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

(Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenylbenzyl)-1,2,4- oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-

5 phenoxybenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

(Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(cyclohexylmethylen)-1,2,4-

oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-

valyl-N-[1-(3-(5-(3-trifluoromethylidimethylmethylen)-1,2,4-oxadiazolyl]carbonyl)-2-

(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(1-

10 naphylmethylene)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

(Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-pyridylmethyl)-1,2,4-oxadiazolyl]carbonyl)-

2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-

diphenylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

(Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-dimethylaminobenzyl)-1,2,4-

15 oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; 2-(5-

[(Benzylloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-

(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)- (S)-2-

methylpropyl]acetamide; 2-(5-Amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-

pyrimidinyl]-N-[1-(3-(5- (3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-

20 methylpropyl]acetamide; 2-(5-[(Benzylloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-

1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-

(S)-2-methylpropyl]acetamide; 2-(5-Amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-

pyrimidinyl]-N-[1-(2-(5- (3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-

methylpropyl]acetamide; (Pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(2-(5-(3-

25 methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide; (Pyrrole-2-

carbonyl)-N-(benzyl)glycyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)]-1,2,4-oxadiazolyl)-

(S)-methylpropyl]amide; (2S,5S)-5-Amino-1,2,4,5,6,7-hexahydroazepino-[3,2,1]-indole-

4-one-carbonyl -N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-(R,S)-2-

methylpropyl]amide; BTD-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-

30 methylpropyl]amide; (R,S)-3-Amino-2-oxo-5-phenyl-1,4,-benzodiazepine-N-[1-(2-(5-(3-

methylbenzy l)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

(Benzylloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide; (Benzylloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide; Acetyl-2-L-(2,3-dihydro-1H-indole)-

5 N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide; 3-(S)-(Benzylloxycarbonyl)amino)- ϵ -lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3-(S)-(Amino)- ϵ -lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide

10 trifluoroacetic acid salt; 3-(S)-[(4-morpholino carbonyl-butanoyl)amino]- ϵ -lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(R,S)-methylpropyl]acetamide; 6-

[4-Fluorophenyl]- ϵ -lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 2-(2-(R,S)-Phenyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 2-(2-(R,S)-phenyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-

15 oxadiazolyl]hydroxymethyl)-2-(S)-methylpropyl]acetamide; 2-(2-(R,S)-Benzyl-4-

oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-acetamide; 2-(2-(R,S)-Benzyl-4-oxothiazolidin-3-yl oxide]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(R,S)-methylpropyl]acetamide;

(1-Benzoyl-3,8-quinazolinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-

20 oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; (1-Benzoyl-3,6-piperazinedione)-

N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

(1-Phenyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-

oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; [(1-Phenyl-3,6-piperazinedione)-

N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)]-2-(S)-

25 methylpropyl]acetamide; 3-[(Benzylloxycarbonyl)amino]-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3-

[(Benzylloxycarbonyl)amino]-7-piperidinyl-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3-(Carbomethoxy-quinolin-

2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-

30 methylpropyl]acetamide; 3-(Amino-quinolin-2-one)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3-[(4-Morpholino)aceto]amino-

quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3,4-Dihydro-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-Acetyl-3-(4-fluorobenzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-Acetyl-3-(4-dimethylamino benzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-Acetyl-3-(4-carbomethoxy benzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-Acetyl-3-[(4-pyridyl)methylene]piperazine-2,5-dione-N-[1-(2-(5-(3-methyl benzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Benzyl-3-(R)-benzyl-piperazine-2,5,-dione]-N-[1-(2-[5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Benzyl-3-(S)-benzyl piperazine-2,5,-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Benzyl-3(R)-benzylpiperazine-2,5,-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Benzyl-3-(S)-benzylpiperazine-2,5,-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Benzyl-3-(S)-benzylpiperazine-2,5,-dione]-N-[1-(3-(5-(2-dimethylaminoethyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Methyl-3-(R,S)-phenylpiperazine-2,5,-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[[Methyl-3-(R,S)-phenyl piperazine-2,5,-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-(4-Morpholino ethyl)3-(R)-benzyl piperazine-2,5,-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(R,S)-Phenyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(R)-Benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(S)-Benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(S)-Benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1 ,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(R)-Benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1 ,2,4-

oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-Benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; and 1-Benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethyl benzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide,

5 pharmaceutically acceptable salts thereof, and combinations thereof.

9. The method of claim 8, in which the effective amount is between about 0.001 and about 7 g/kg body weight.

10. The method of claim 1, in which the subject is a human.

11. The method of claim 1, in which the disease is at least one of cancer, 10 autoimmune disease, neurodegenerative disease, myocardial infarction, stroke, sepsis, ischemia reperfusion injury, toxin induced liver injury, or AIDS.

12. The method of claim 1, in which the therapeutically effective amount is sufficient to provide about 10 pM to about 2 mM of the inhibitor in the biological fluid of the subject.

15. 13. The method of claim 12, in which the biological fluid is blood.

14. The method of claim 1, in which the therapeutically effective amount is sufficient to provide about 5 μ M to about 200 μ M in the biological fluid of the subject.

20. 15. The method of claim 1, in which the administering is parenterally, orally, vaginally, rectally, nasally, buccally, intravenously, intramuscularly, subcutaneously, intrathecally, epidurally, transdermally, intracerebroventricularly, by osmotic pump, or combinations thereof.

16. The method of claim 1, in which the therapeutically effective amount is administered between about once daily to about once hourly.

25. 17. The method of claim 2, in which the monitoring is performed on a biopsy from the subject.

18. A method of prophylactically treating an individual at risk for a pathological condition that is precipitated at least in part by excessive apoptosis, comprising:

30. administering to an individual a therapeutically effective amount of at least one agent exhibiting mammalian α_1 -antitrypsin or α_1 -antitrypsin-like activity.

19. A method for inhibiting apoptosis in an in vitro mammalian cell culture,

an ex vivo mammalian tissue culture, or mammalian organ comprising:

providing to a cell culture, tissue culture, or organ an amount of a serine protease inhibitor sufficient to inhibit apoptosis in said cell culture, tissue culture, or organ wherein a measured amount of apoptosis is indicative of apoptosis activity.

5 20. The method of claim 19, wherein the mammalian organ is a donor organ.

21. A method of inhibiting apoptosis, comprising providing a serine protease inhibitor to a cell and measuring a decrease in apoptosis.

10 22. The method of claim 21, in which the serine protease inhibitor is α_1 -antitrypsin, variant of α_1 -antitrypsin, an antithrombin G agent, an antitryptase TL-2 agent, an antifactor Xa agent, an antielastase agent, an antiproteinase-3 agent, substituted oxydiazole, substituted thiadiazole, substituted triazole peptoids, or combinations thereof.

23. The method of claim 22, in which the serine protease inhibitor is derivatized by esterification, acetylation, or amidation.

15 24. The method of claim 23, in which the amount is sufficient to bring the concentration in the blood to between about 5 μ M and about 200 μ M.

20 25. The method of claim 21, in which the serine protease inhibitor is (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-phenylethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(methyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(difluoromethyl)-1,2,4-oxadiazolyl) carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(benzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(benzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(3-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(2,6-difluorobenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(trans-styryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-

Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(trans-4-Trifluoro methylstyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(trans-4-Methoxystyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-

5 Methylpropyl]-L-Prolinamide; (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(3-
Thienylmethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide;
(Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(5-(Phenyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-
methylpropyl]-L-prolinamide; and (Benzylloxycarbonyl)-L-Valyl-N-[1-(3-(3-
Phenylpropyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-Methylpropyl]-L-Prolinamide,
Benzylloxycarbonyl-L-valyl-N-[1-(2-[5-(3-methylbenzyl)-1,3,4-oxadiazolyl] carbonyl)-2-
10 (S)-methylpropyl]-L-prolinamide, Benzylloxycarbonyl-L-valyl-N-[1-(2-(3-methylbenzyl)-
1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; Benzylloxycarbonyl-L-
valyl-N-[1-(2-(5-(methyl)-1,3,4-oxadiazoly]carbonyl)- 2-(S)-methylpropyl]-L-
prolinamide; Benzylloxycarbonyl)-L-valyl-N-[1-(2-(5-(3-trifluoromethylbenzyl)-1,3,4-
15 oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-
valyl-N-[1-(2-(5-(4-Dimethylamino benzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-
methylpropyl]-L-prolinamide; Benzylloxycarbonyl)-L-valyl-N-[1-(2-(5-(1-naphthylenyl)-
1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-
L-valyl-[1-(3-(5-(3,4-methylenedioxybenzyl)-1,2,4 -oxadiazolyl]carbonyl)-2-(S)-
20 methylpropyl]-L-prolinamide; Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-
dimethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
(Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethoxybenzyl)-1,2,4-
oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-
valyl-N-[1-(3-(5-(3,5-dtrifluoromethylbenzyl)-1,2,4 -oxadiazolyl]carbonyl)-2-(S)-
25 methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-
methylbenzyl)-1,2,4-oxadiazolyl] carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
(Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(biphenylmethine)-1,2,4-oxadiazolyl
]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-
(4-phenylbenzyl)-1,2,4-oxadiazolyl] carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
(Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenylbenzyl)-1,2,4- oxadiazolyl]carbonyl)-
30 2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-
phenoxybenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

(Benzylloxycarbonyl)-L-valyl-N-[1-(3-(cyclohexylmethylene)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethyldimethylmethylen)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(1-naphthylmethylene)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
5 (Benzylloxycarbonyl)-L-valyl-N-[1-(3-(3-pyridylmethyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (Benzylloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-diphenylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
(Benzylloxycarbonyl)-L-valyl-N-[1-(3-(4-dimethylaminobenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide; 2-(5-[(Benzylloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-2-methylpropyl]acetamide; 2-(5-Amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 2-(5-[(Benzylloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-2-methylpropyl]acetamide; 2-(5-Amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-methylpropyl]acetamide; (Pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide; (Pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)]-1,2,4-oxadiazolyl)-2-(S)-methylpropyl]amide; (2S,5S)-5-Amino-1,2,4,5,6,7-hexahydroazepino-[3,2,1]-indole-4-one-carbonyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-(R,S)-2-methylpropyl]amide; BTD-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide; (R,S)-3-Amino-2-oxo-5-phenyl-1,4,-benzodiazepine-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;
25 (Benzylloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide; (Benzylloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide; Acetyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide; 3-

(S)-(Benzylloxycarbonyl)amino)- ϵ -lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3-(S)-(Amino)- ϵ -lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide trifluoroacetic acid salt; 3-(S)-[(4-morpholino carbonyl-butanoyl)amino]- ϵ -lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(R,S)-methylpropyl]acetamide; 6-[4-Fluorophenyl]- ϵ -lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 2-(2-(R,S)-Phenyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 2-(2-(R,S)-phenyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]hydroxymethyl)-2-(S)-methylpropyl]acetamide; 2-(2-(R,S)-Benzyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-acetamide; 2-(2-(R,S)-Benzyl-4-oxothiazolidin-3-yl oxide]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(R,S)-methylpropyl]acetamide; (1-Benzoyl-3,8-quinazolinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; (1-Benzoyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; (1-Phenyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; [(1-Phenyl-3,6-piperazinedione)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)]-2-(S)-methylpropyl]acetamide; 3-[(Benzylloxycarbonyl)amino]-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3-[(Benzylloxycarbonyl)amino]-7-piperidinyl-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3-(Carbomethoxy-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3-(Amino-quinolin-2-one)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3-[(4-Morpholino)aceto]amino-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 3,4-Dihydro-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-Acetyl-3-(4-fluorobenzylidene)piperazine-2,5-piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-Acetyl-3-(4-dimethylamino benzylidene)piperazine-2,5-

dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-Acetyl-3-(4-carbomethoxy benzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-Acetyl-3-[(4-pyridyl)methylene]piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Benzyl-3-(R)-benzylpiperazine-2,5,-dione]-N-[1-(2-[5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Benzyl-3-(S)-benzyl piperazine-2,5,-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Benzyl-3(R)-benzylpiperazine-2,5,-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Benzyl-3-(S)-benzylpiperazine-2,5,-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Benzyl-3-(S)-benzylpiperazine-2,5,-dione]-N-[1-(3-(5-(2-dimethylaminoethyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-Methyl-3-(R,S)-phenylpiperazine-2,5,-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[-Methyl-3-(R,S)-phenyl piperazine-2,5,-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-(4-Morpholino ethyl)3-(R)-benzyl piperazine-2,5,-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(R,S)-Phenyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(R)-Benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(S)-Benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(S)-Benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(R)-Benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-Benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; and 1-Benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide, or pharmaceutically acceptable salts thereof, or combinations thereof.

26. A method of sustaining antitrypsin activity in the blood comprising administering to a subject sufficient α_1 -antitrypsin to replace inactivated α_1 -antitrypsin.

27. A method of sustaining antitrypsin activity in the blood comprising administering a therapeutically effective amount of a variant antitrypsin that is resistant to 5 inactivation by free radicals or a synthetic α_1 -antitrypsin that is resistant to inactivation by free radicals.

28. The method of claim 27, in which the variant antitrypsin is Val³⁵⁸-antitrypsin, Ile³⁵⁸-antitrypsin, Leu³⁵⁸-antitrypsin, Phe³⁵⁸-antitrypsin, Tyr³⁵⁸-antitrypsin, Trp³⁵⁸-antitrypsin, or combinations thereof.

ABSTRACT

The instant invention provides a method of treating an animal suffering a disease characterized by excessive apoptosis by administering a therapeutically effective amount of at least one serine protease inhibitor and thereafter monitoring a decrease in apoptosis. 5 The inhibitor of the invention includes α_1 -antitrypsin or an α_1 -antitrypsin-like agent, including, but not limited to oxidation-resistant variants of α_1 -antitrypsin, and peptoids with antitrypsin activity. The diseases treatable by the invention include cancer, autoimmune disease, sepsis neurodegenerative disease, myocardial infarction, stroke, 10 ischemia-reperfusion injury, toxin induced liver injury and AIDS. The method of the invention is also suitable for the prevention or amelioration of diseases characterized by excessive apoptosis.

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EFFECTS OF AAT ON RCGC AFTER 20 HRS SERUM-WITHDRAWAL

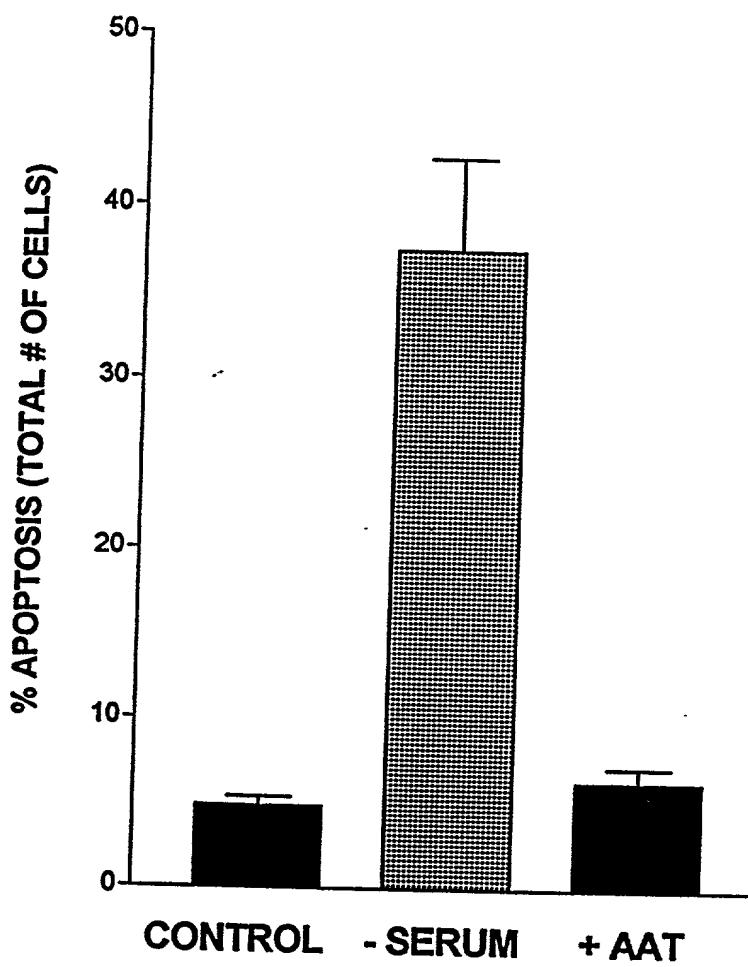


Figure 1

Effect of AAT on apoptosis in RCG neurons

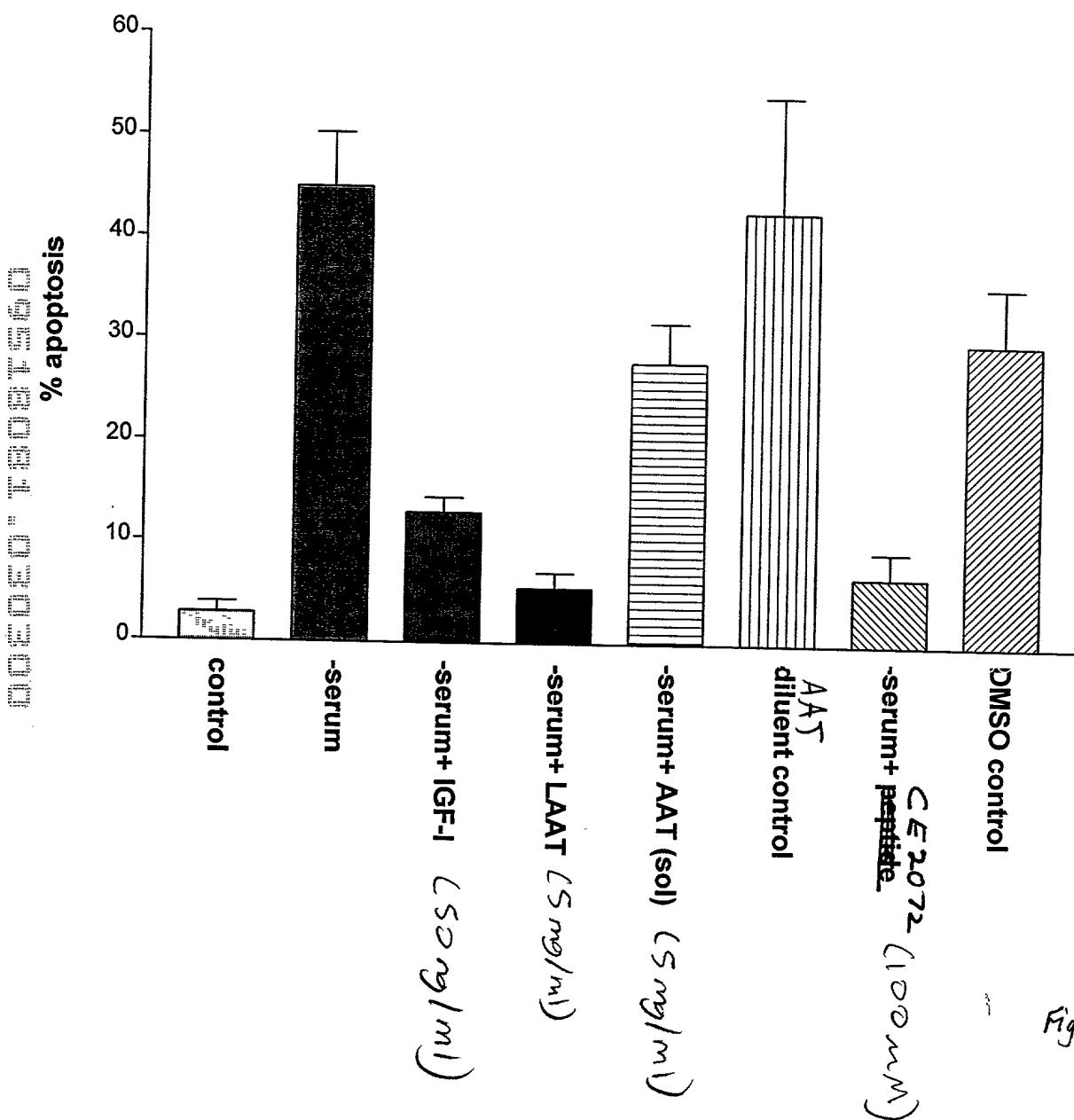


Figure 2

Docket No.: 114232-104

DECLARATION AND POWER OF ATTORNEY

As below named inventor, I hereby declare that:

My residence, post office and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter claimed and for which a patent is sought on the invention entitled **METHODS AND COMPOSITIONS USEFUL IN INHIBITING APOPTOSIS**, the specification of which [X] is attached hereto OR [] was filed on, or Application Serial No. _____ and was amended on (if applicable).

I/We hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I/We acknowledge the duty to disclose information which is known to me to be material to patentability in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

I/We hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):			Priority Claimed	
<u>Number</u>	<u>Country</u>	<u>Day/Month/Year filed</u>	<u>Yes</u>	<u>No</u>

I hereby claim the benefit under 35 USC Section 119(e) of any United States provisional application(s) listed below.

Prior Provisional Application(s):

<u>Application Number</u>	<u>Filing Date</u>
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60/123,167	March 5, 1999
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I/We hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Prior U. S. Application(s):

<u>Serial No.</u>	<u>Filing Date</u>	<u>Status: Patented, Pending, Abandoned</u>
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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